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Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin

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Keitaro Senoo: Nothing to declare.

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Abstract

Introduction: Various bleeding risk prediction schemes, such as the HAS-BLED, ATRIA and ORBIT scores have been proposed in patients with atrial fibrillation (AF). We compared the relative predictive values of these bleeding risk scores for clinically relevant bleeding, as well as the relationship of ATRIA and ORBIT scores to the quality of anticoagulation control on warfarin, as reflected by time in therapeutic range (TTR).

Methods: A post-hoc ancillary analysis of 'clinically relevant bleeding' and 'major bleeding' events amongst 2293 patients on warfarin therapy in the AMADEUS trial.

Results: Only HAS-BLED was significantly predictive for clinically relevant bleeding, and all 3 risk scores were predictive for major bleeding. The predictive performance of HAS-BLED was modest, as reflected by c-indexes of 0.59 ($p<0.001$) and 0.65 ($p<0.002$), for clinically relevant bleeding and major bleeding, respectively. The HAS-BLED score performed better than ATRIA (P=0.002) or ORBIT (P=0.001) in predicting any clinically relevant bleeding. Only the HAS-BLED score was significantly associated with the risk for both bleeding outcomes on Cox regression analysis (any clinically relevant bleeding; hazard ratio [HR] 1.85, 95%CI 1.43-2.40, $p<0.001$, and major bleeding; HR 2.40, 95%CI 1.28-4.52, p=0.007).

There were strong inverse correlations of ATRIA and ORBIT scores to TTR as a continuous variable ('low risk' ATRIA, r= -0.96; P=0.003; ORBIT, r= -0.96; p=0.003). Improvement in the predictive performance for both ATRIA and ORBIT scores for any clinically relevant bleeding was achieved by adding TTR to both scores, with significant differences in c-indexes (p=0.001 and p=0.002, respectively), NRI and IDI (both $p<0.001$).

Conclusion: All three bleeding risk prediction scores demonstrated modest predictive ability for bleeding outcomes, although the HAS-BLED score performed better than either the

ATRIA or ORBIT scores. Significant improvements in both ATRIA and ORBIT score prediction performances were achieved by adding TTR to both scores.

Key words bleeding, HAS-BLED, ORBIT, ATRIA, risk assessment, anticoagulation

Introduction

Various bleeding risk scores have been derived in general populations undergoing anticoagulation, and validated in patients with atrial fibrillation (AF); for example, the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol)[1]; and the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score.[2] More recently, a new bleeding prediction score, the ORBIT (Outcomes Registry for Better Informed Treatment) score, was developed from a large observational cohort of atrial fibrillation patients [3], and validated in the ROCKET-AF trial cohort [4]. The ORBIT score was proposed as a simple bedside score, to be used with any oral anticoagulant (Vitamin K Antagonist (VKA, eg. warfarin) or non-VKA oral anticoagulant (NOAC)). In patients taking VKA, both the ATRIA and ORBIT scores do not consider quality of anticoagulation control, as reflected by the time in therapeutic range (TTR) whilst the HAS-BLED score includes this within the L criterion ('labile INR'). This is despite TTR being strongly correlated to the risk of serious bleeding in patients taking VKA[5, 6].

In this study, we tested the hypothesis that the HAS-BLED score would perform at least as well as the ATRIA and new ORBIT scores in predicting the principal trial safety outcome of any clinically relevant bleeding, in addition to the secondary endpoint of major bleeding**.** Second, we hypothesised that the addition of TTR to the ATRIA and ORBIT scores would identify additional patients at high risk of clinically relevant bleeding. We tested these hypothesis in a post-hoc analysis of warfarin-treated patients from the AMADEUS trial

(Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial [7].

Methods

The design and results of the AMADEUS trial have previously been described. [7, 8] In brief, this was a multicentre, randomized, open-label non-inferiority study with blinded assessment of outcome that compared fixed-dose idraparinux with conventional anticoagulation with dose-adjusted oral VKA for the prevention of thromboembolism in patients with atrial fibrillation and an indication for long-term anticoagulation. Eligible patients had ECG-documented nonvalvular atrial fibrillation and an indication for long-term anticoagulation, based on the presence of at least one of the following risk factors: previous ischemic stroke, transient ischemic attack (TIA) or systemic embolism, hypertension requiring drug treatment, left ventricular dysfunction, age >75 years, or age 65-75 with either diabetes mellitus or symptomatic coronary artery disease. Exclusion criteria included the inability to provide consent, contraindication or other requirement for anticoagulation, calculated creatinine clearance of <10 mL/min, breastfeeding, pregnancy and recent or anticipated invasive procedures with potential for uncontrolled bleeding. There was blinded assessment of trial outcomes, and for this ancillary analysis, outcomes were analysed for the warfarin arm of the trial only, as the development of idraparinux has been discontinued and thus, less relevant for our clinical practice.

Bleeding Risk Scores Assessment

The acronym HAS-BLED represents each of the bleeding risk factors and assigns 1 point for the presence of each of the following bleeding risk factors: Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal renal and/or liver function, previous Stroke, Bleeding history or predisposition, Labile INR (international normalized ratio; only applies to a VKA user – otherwise not applicable for a non-VKA user), Elderly (age ≥65 years), and concomitant Drugs and/or alcohol excess. In the present analysis, the variable "labile international normalized ratio (INR)" was defined for a TTR<60%. For this study, we used each patient's first 5 INR measurements following study entry to calculate the TTR. A HAS-BLED score of 0-2 was categorized as "low risk", while HAS-BLED ≥3 was categorized as "high risk".

The ATRIA score was developed from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)[2] study cohort and calculated using the following: anaemia (haemoglobin <13 g/dl in men and <12 g/dl in women) (3 points), severe renal disease (estimated glomerular filtration rate <30 ml/min/1.73m^2) (3points), age ≥75 years (2 points), prior bleeding and hypertension. An ATRIA score of 0-3 is defined as "low risk", while a score=4 was "Intermediate risk" and a score ≥5 was "high risk".

The ORBIT score was developed from the "Outcomes registry for better informed treatment of atrial fibrillation" (ORBIT-AF) registry,[3] and calculated as follows: 1 point each for age older than 74, insufficient kidney function (estimated glomerular filtration rate < 60 ml/min/1.73m^2) and treatment with any antiplatelet, while 2 points were assigned to a positive clinical history for bleeding and the presence of anaemia or abnormal haemoglobin (<13 mg/dL for males and <12 mg/dL for females). An ORBIT score 0-2 was "low risk", while

"intermediate risk" was a score of 3 and a score ≥4 was "high risk". In the present study, none of the patients had a history of alcohol abuse or prior major bleeding at study entry, as these were criteria for exclusion from the AMADEUS trial, and therefore those components were categorised as 0.

Definitions of endpoints

This post-hoc analysis of the AMADEUS trial used pooled data from the VKA arm on an intention to treat basis. The principal adjudicated safety outcome of the present analysis was 'any clinically relevant bleeding', which was defined as major bleeding and/or non-major clinically relevant bleeding. The latter was defined as overt bleeding that did not satisfy the criteria for major bleeding but that met pre-defined criteria and included repetitive epistaxis for more than 5 min at least twice in 24 h, haematuria (spontaneous or lasting more than 24 h), hematemesis, and subcutaneous haematomas of more than 25 cm^2 if spontaneous, or more than 100 cm^2 if after trauma. Major bleeding was defined as bleeding that was fatal, intracranial or affecting another critical anatomical site, overt bleeding with a drop of haemoglobin ≥20 g/L or requiring transfusion of two or more units of erythrocytes.

All suspected outcome events were adjudicated by the original AMADEUS central adjudication committee, who were blinded to treatment assignment.

Statistical analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as means and standard deviations (SD). Non-parametric

variables were expressed as median and interquartile range (IQR). Categorical variables, expressed as counts and percentages, were analysed by chi-squared test. Bleeding outcomes by each bleeding risk scheme were calculated as the overall rate of adverse events per 100 patient-years.

A Cox regression analysis was performed to investigate the association between three bleeding risk schemes and bleeding outcomes, such as any clinically relevant bleeding and major bleeding. Pearson correlations and regression analyses were performed between TTR and any clinically relevant bleeding, in relation to the ATRIA and ORBIT scores.

Receiver operating characteristic (ROC) curves were compiled for the three risk scores, according to bleeding outcomes, in order to evaluate their predictive ability using the area under the curve method (AUC, a measure of their c-index). Their respective AUCs were then compared according to De Long, De Long and Clarke-Pearson method.[9] We also tested the predictive ability of the ATRIA and ORBIT scores with and without the addition of TTR, by comparing AUCs as well as calculating the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) using PredicABEL, an R package for the assessment of risk prediction prediction model.[10] [11] A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA), MedCalc v. 15.6 (MedCalc Software, Belgium) and R statistic for Windows 3.2.2.

Results

The AMADEUS study randomized 2293 patients to warfarin (65% male; median age: 71 years, IQR 64-77). In total, 251 (11%) patients experienced at least 1 clinically relevant bleeding event, whilst 39 (1.7%) had at least 1 episode of major bleeding. Demographic and clinical characteristics of the AMADEUS population are summarized in Table 1. Bleeding event rates in the study population, as stratified by the three bleeding scores, are shown in Figure 1.

Predictive performance of HAS-BLED, ATRIA and ORBIT

Median HAS-BLED score in the study cohort was 2 (IQR, interquartile range: 1-2), whilst the median ATRIA score was 1 (IQR: 1-3) and median ORBIT score was 1 (IQR: 0-1). Only HAS-BLED was significantly predictive for clinically relevant bleeding, and all 3 scores were predictive for major bleeding. The predictive performance of HAS-BLED was modest, as reflected by c-indexes of 0.59 ($p<0.001$) and 0.65 ($p<0.002$), for clinically relevant bleeding and major bleeding, respectively. Corresponding c-indexes for the ATRIA score were 0.50 ($p=0.50$, non-significant) and 0.61 ($p=0.02$), respectively. For the ORBIT score, c-indexes were 0.52 ($p=0.30$, non-significant) and 0.61 ($p=0.02$), respectively (see Figure 2).

In a Cox regression analysis, a HAS-BLED score ≥3 was associated with a 1.85-fold greater hazard for any clinically relevant bleeding ($p<0.001$) and a 2.4-fold greater hazard for major bleeding ($p=0.007$). On a similar Cox regression analysis, an ATRIA score ≥4 was not significantly associated with any clinically relevant bleeding ($p=0.54$) but was associated with a 2.4-fold greater hazard of major bleeding ($p=0.03$). An ORBIT score ≥3 was not

significantly associated with any clinically relevant bleeding (p=0.36) but was associated with a 2.9-fold greater hazard of major bleeding (p=0.01) (see Table 2).

Comparison of bleeding scores

The HAS-BLED score performed significantly better than ATRIA (p=0.002) or ORBIT (p=0.001) in predicting any clinically relevant bleeding, as reflected by comparison of AUC analyses (Table 3). The AUCs for ATRIA vs ORBIT were similar (p=0.66). For major bleeding, AUC differences for the 3 scores did not reach statistical significance.

Impact of TTR on the ORBIT and ATRIA scores

Any clinically relevant bleeding in relation to tertiles of Time to Therapeutic Range (TTR) and TTR as a continuous variable, by ORBIT and ATRIA scores are shown in Figure 3.

There was a high absolute event rate for clinically relevant bleeding amongst patients with poor anticoagulation control (TTR<50%; ie. >15 per 100 person-years) even among those categorised as 'low risk' using these 2 scores, whereas there was a strong negative correlation to TTR as a continuous variable (ATRIA, Pearson r= -0.96; P=0.003; ORBIT, r= -0.96; p=0.003). This correlation was also significant for the ATRIA intermediate/high score group (r= - 0.85; p=0.03), with a non-significant trend with the ORBIT intermediate/high score group (r= - 0.77; p=0.07).

The improvements in prediction performance by adding TTR to the ATRIA or ORBIT scores are shown in Table 4. For the ATRIA score, adding TTR would result in a significant improvement in AUC (p=0.001), with a NRI of 0.26 (p<0.001) and an IDI of 0.0066 (p<0.001),

compared to ATRIA score without TTR. For the ORBIT score, the AUC difference was also significant (p=0.002), with NRI of 0.26 (p<0.001) and IDI of 0.0065 (p<0.001).

Discussion

In this study, we compared the ability of the HAS-BLED, ATRIA and ORBIT scores to predict bleeding events in a clinical trial cohort of atrial fibrillation patients taking warfarin, and also examined the relationship of these scores to TTR. We show that the HAS-BLED score performed better than the ATRIA and ORBIT scores, especially in predicting clinically relevant bleeding events. Second, there was a strong correlation of TTR with clinically relevant bleeding events in patients assessed by the ATRIA and ORBIT, even amongst those categorised as 'low risk'. Third, we show clear improvements in prediction performance by adding TTR to both the ATRIA and ORBIT scores.

Despite the increasing use of NOACs, the VKAs are still very widely used worldwide and increasing attention has been directed to the importance of good anticoagulation control, as reflected by the TTR. The HAS-BLED score accounts for 'labile INRs' (the 'L' criterion – which is only applicable for a VKA-taking patient) by giving it one point, but the ATRIA and ORBIT scores do not recognise the importance of this criterion when calculating bleeding risk. This is despite evidence that labile INRs (whether defined by poor TTRs or other measures indicative of poor anticoagulation control [6, 12, 13]) are a strong predictor of excess bleeding risk. Indeed, we demonstrate that the risk of any clinically relevant bleeding (and major bleeding) decreases overall with better anticoagulation control. Importantly, there was high

absolute event rate for clinically relevant bleeding amongst the patients with poor anticoagulation control (TTR<50%; >15 per 100 person-years) even amongst those categorised as 'low risk' using the ATRIA and ORBIT scores, as well as a strong negative correlation to TTR, when analysed as a continuous variable with these 2 bleeding scores. Significant improvements in score predictive performance were gained by adding TTR to both ATRIA and ORBIT scores for clinically relevant bleeding, as reflected by a significant difference in AUC, NRI and IDI. Thus, both these scores may perform suboptimally in identifying serious bleeding risk in a patient on VKA, unless they are re-calibrated taking labile INRs (or TTRs) into consideration. The HAS-BLED score already considers 'labile INR' as one of its criteria, which is applicable only for a VKA user (whilst the L criterion is not applicable if a NOAC is used).

Since its original description in the EuroHeart survey, the HAS-BLED score has been validated in both large real-world and clinical trial populations, and recently reviewed in a comprehensive European consensus document.[14] Prior direct comparisons with other bleeding prediction scores, such as HEMORR$_2$HAGES and ATRIA, have shown that the HAS-BLED score is as good as – and possibly better – than other scores in the evaluation of bleeding risk. [8, 15] The more recently proposed ORBIT score was derived from a large industry-sponsored registry, and validated in the ROCKET-AF trial cohort, with the claim to be simple and applicable to all anticoagulants, whether VKA or NOAC. [3]

As shown in the present study, all three bleeding scores showed modest discriminatory capacity for bleeding outcomes, as reflected by c-indexes <0.70, although HAS-BLED was the only score predictive of both clinically relevant and major bleeding. For major bleeding

events, all three scores demonstrated similar predictive ability, but with c-indexes <0.70. These c-indexes (approximately 0.6) are perhaps typical of clinical risk scores based on clinical features, including those used for stroke risk prediction such as the $CHADS_2$ and CHA_2DS_2-VASc scores. Rather then undue focus on statistical significance in predicting the high risk patients who develop an event, the clinical applicability of bleeding risk scores requires attention to the reversible risk factors for bleeding[16], especially since both stroke and bleeding risks are closely associated.

For example, the HAS-BLED score is used to 'flag up' the patient potentially at high risk of bleeding, who may require more careful review and followup – and to direct attention to the potentially reversible bleeding risk factors, such as uncontrolled hypertension (the H criterion), labile INRs (the L criterion) and concomitant drugs (aspirin, NSAIDs) or excess alcohol (the D criterion) that the responsible clinician can address. Indeed, this is the approach recommended in current guidelines[12, 17]. Of note, the ORBIT score does not include uncontrolled hypertension, labile INRs, alcohol excess or concomitant NSAIDs within its criteria[16].

A high HAS-BLED score is not a reason to withhold OAC, as such patients derive an even greater net clinical benefit when balancing stroke prevention against the potential for increased serious bleeding[18, 19], an approach also recommended in guidelines[12, 17]. The HAS-BLED score has also been validated for predicting bleeding in patients on no antithrombotic therapy or aspirin, as well as on OAC, whether VKA or non-VKA types of anticoagulation, as well as atrial fibrillation and non-atrial fibrillation patients. Thus, the HAS-BLED score would be applicable thoughout the patient pathway, which is an important consideration given

that risk assessment is not a static process and patient's risk evolves over time. The ORBIT score has only been validated in anticoagulated patients.

Limitations

These results are based on a post-hoc analysis of the AMADEUS trial, and should be interpreted as hypothesis-generating. The AMADEUS trial population was perhaps at relatively low risk for bleeding events when compared with atrial fibrillation patients in clinical practice, since patients with a history of major bleeding events were excluded from this trial.

In conclusion, the HAS-BLED, ATRIA and ORBIT bleeding risk scores all demonstrated modest performance in predicting bleeding outcomes, although the HAS-BLED score performed significantly better than the ORBIT and ATRIA scores, in predicting clinically relevant bleeding. TTR was strongly correlated with clinically relevant bleeding events in patients assessed by the ATRIA and ORBIT scores, even amongst those categorised as 'low risk'. Significant improvements in both ATRIA and ORBIT score prediction performances were achieved by considering quality of anticoagulation control, by adding TTR to both scores.

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Table 1: Demographic and clinical characteristics of patients on warfarin (n=2293)

Age, years	71 (64-77)
Males	1501 (65.5)
Body Mass Index	28 (25.3-31.2)
Type of AF	
- Paroxysmal	813 (35.5)
- Persistent	214 (9.3)
- Permanent	1258 (54.9)
Hypertension	1764 (76.9)
Heart Failure	543 (23.7)
Diabetes Mellitus	450 (19.6)
Coronary Artery Disease	718 (31.3)
Stroke/TIA	575 (25.1)
Creatinine clearance mls/min	71.4 (55.2-91.7)
Time in therapeutic range (TTR)	58 (45-70)
Use of Aspirin	379 (16.5)
Use of NSAID	123 (5.4)
CHA_2DS_2-VASc score (IQR)	3 (2-4)
1 (%)	180 (7.8)
2 (%)	481 (21)
3 (%)	567 (24.7)
4 (%)	501 (21.8)
5 (%)	321 (14)
6 (%)	160 (7)
7 (%)	68 (3)
8 (%)	14 (0.6)
9 (%)	1 (0.0)
HAS-BLED score	2 (1-2)

Low: <3	1739 (75.9)
High: ≥3	553 (24.1)
ATRIA score	1 (1-3)
Low: 0-3	2042 (90.1)
Intermediate: 4	98 (4.3)
High: ≥5	127 (5.6)
ORBIT score	1 (0-1)
Low: 0-2	2106 (92.9)
Intermediate: 3	129 (5.7)
High: ≥4	32 (1.4)

AF= Atrial Fibrillation; IQR= interquartile range; NSAIDS= Non-Steroidal Anti-Inflammatory Drugs; TIA= transient ischemic attack; TTR= time in therapeutic range

CHA_2DS_2-VASc score= Congestive heart failure, Hypertension, Age≥ 75 years (2 points), Diabetes mellitus, previous Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65-74 years, and female gender

HAS-BLED score= Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), Elderly (age≥65 years), drugs or alcohol concomitant

ATRIA score= anemia (hemoglobin <13 g/dl in men and <12 g/dl in women) (3 points), severe renal disease (glomerular filtration rate <30 ml/min/1.73m^2 or dialysis dependent) (3points), age≥75 years (2 points), prior bleeding and hypertension.

ORBIT score= Older age (≥ 74 years), reduced hemoglibin/Anemia [(hemoglobin <13 g/dl in men and <12 g/dl in women) or (hematocrit <40% for males and <36% for females) (2 points)], Bleeding history (2 points), Insufficient kidney function [glomerular filtration rate <60 ml/min/1.73m^2], Treatment with Antiplatelet.

Table 2: Cox regression analysis of HAS-BLED, ATRIA and ORBIT score for bleeding outcomes

	Any clinically relevant bleeding		Major bleeding	
	HR (95%CI)	P value	HR (95%CI)	P value
HAS-BLED high score (≥3)	1.85 (1.43-2.40)	<0.001	2.40 (1.28-4.52)	0.007
ATRIA Inter/high score (≥4)	1.13 (0.76-1.69)	0.54	2.40 (1.10-5.22)	0.03
ORBIT Inter/high score (≥3)	1.23 (0.79-1.93)	0.36	2.93 (1.29-6.64)	0.01

HR; hazard ratio, CI; Confidence Interval

Table 3: Comparison of AUCs for HAS-BLED, ATRIA and ORBIT scores

	Any clinically relevant bleeding			Major bleeding		
	AUC difference (95%CI)	Z score	P value	AUC difference (95%CI)	Z score	P value
Comparison						
HAS-BLED vs. ATRIA	0.09 (0.03-0.15)	3.11	0.002	0.04 (-0.06-0.14)	0.80	0.42
HAS-BLED vs. ORBIT	0.07 (0.03-0.12)	3.39	0.001	0.04 (-0.06-0.14)	0.74	0.46
ATRIA vs. ORBIT	0.02 (-0.05-0.08)	0.44	0.66	0.002 (-0.05-0.05)	0.07	0.94

AUC; area under the curve, CI; confidence interval

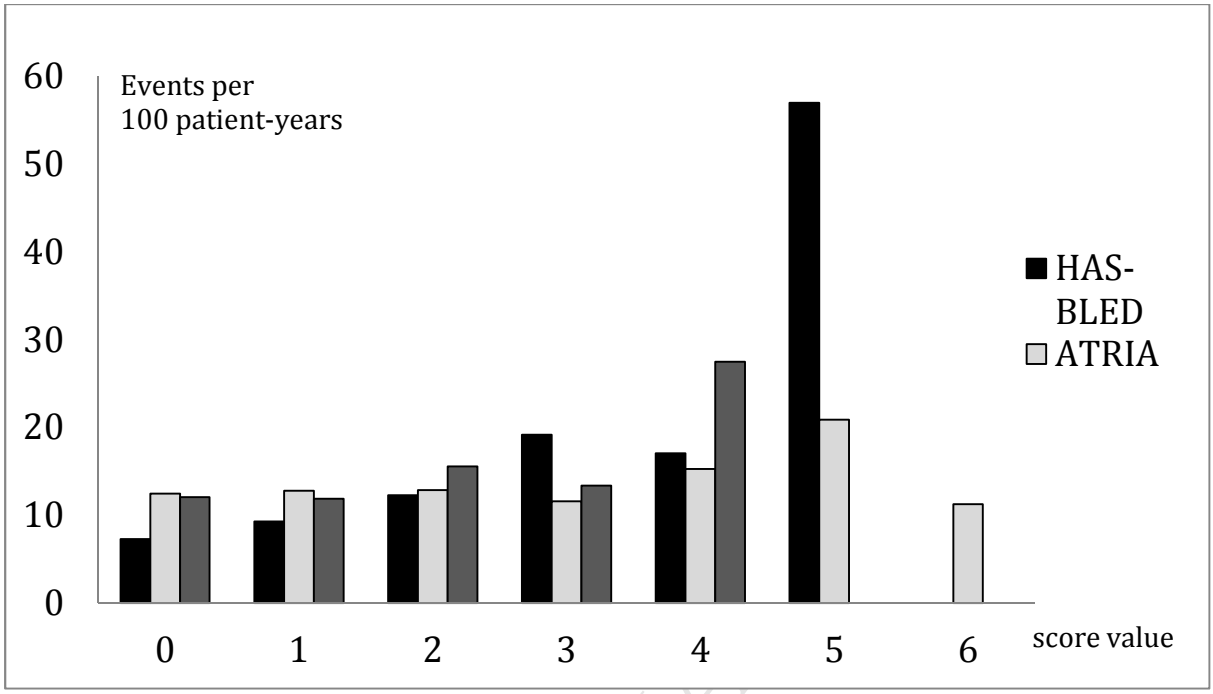
Table 4: Prediction performance by adding TTR to the ATRIA and ORBIT scores

	ATRIA+TTR vs ATRIA				**ORBIT+TTR vs ORBIT**
	Any clinically relevant bleeding	P value	Major bleeding	P value	Any clinically relevant bleeding
AUC difference	0.064	0.001	0.039	0.251	0.054
NRI	0.260	<0.001	0.348	0.02	0.260
IDI	0.0066	<0.001	0.002	0.065	0.0065

AUC; Area under the curve, NRI; Net reclassification improvement, IDI; Integrated discriminant improvement

Figure 1: Incidence rate of bleeding outcomes according to HAS-BLED, ATRIA and ORBIT scores

a) Any clinically relevant bleeding



b) Major bleeding

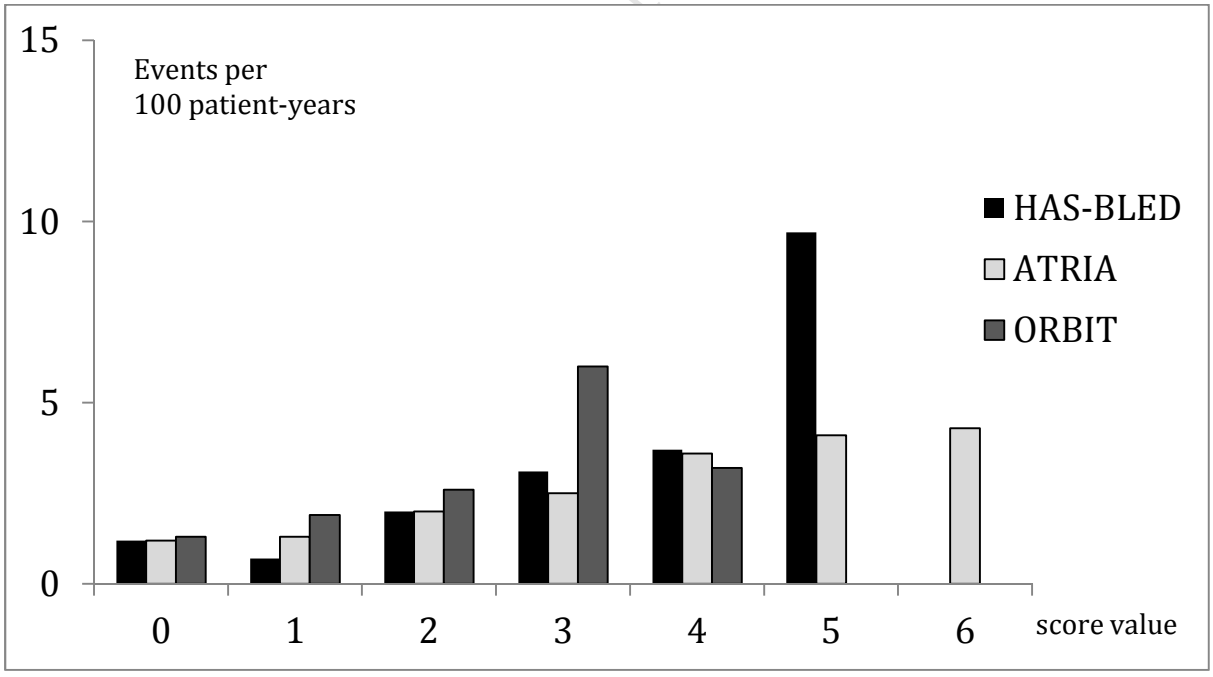
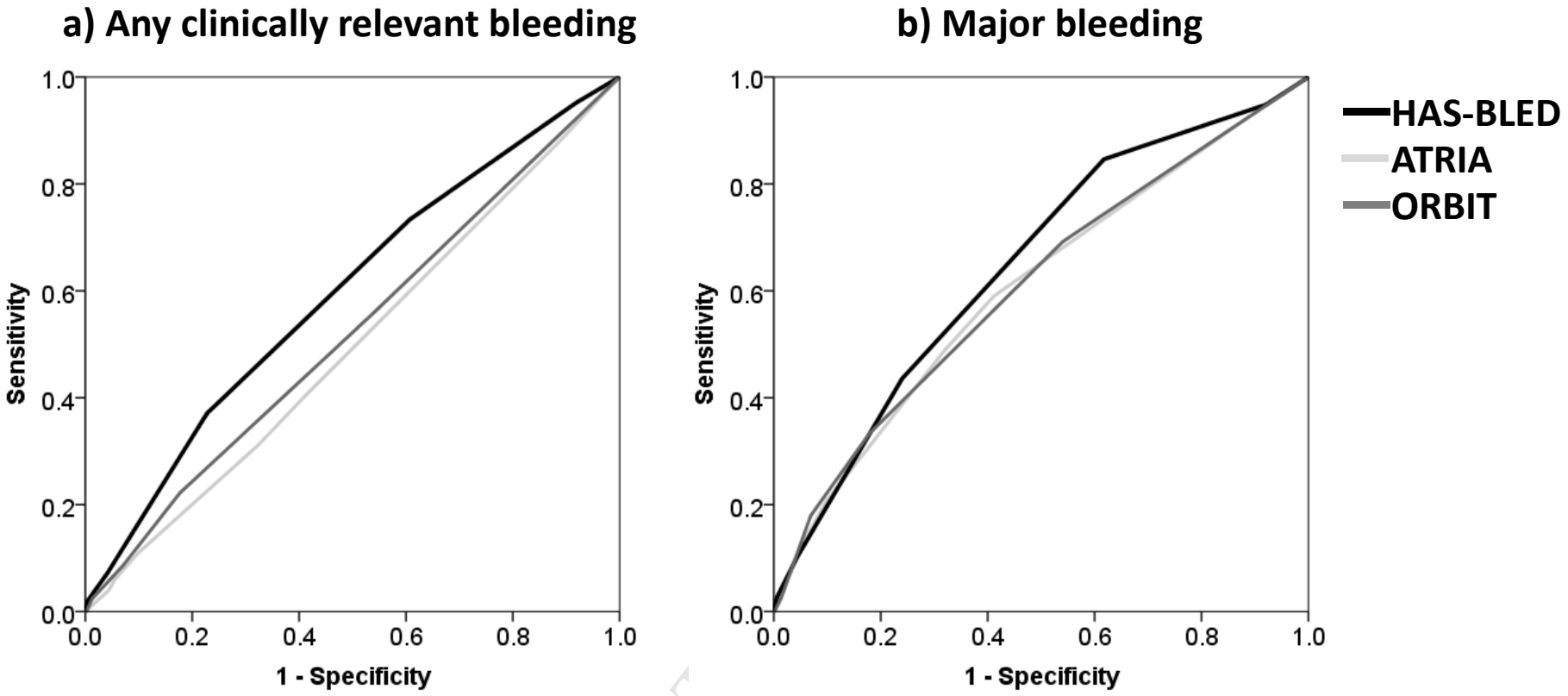


Figure 2: AUC (area under the curve) for bleeding endpoints with the 3 bleeding risk scores

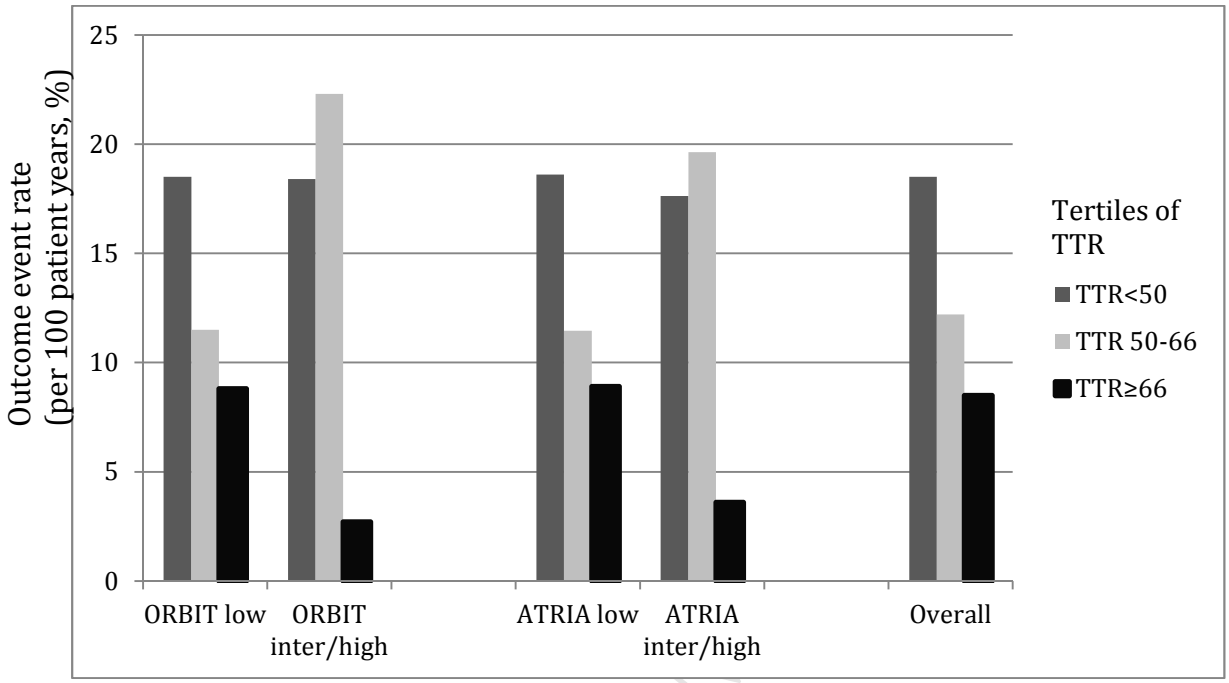


	Any clinically relevant bleeding				Major bleeding			
AUC Analysis	AUC	95%CI	SE	P value	AUC	95%CI	SE	P value
HAS-BLED	0.59	0.56-0.63	0.02	<0.001	0.65	0.56-0.73	0.04	0.002
ATRIA	0.54	0.51-0.57	0.02	0.02	0.61	.51-0.70	0.05	0.02
ORBIT	0.52	0.48-0.56	0.02	0.30	0.61	0.51-0.70	0.05	0.02

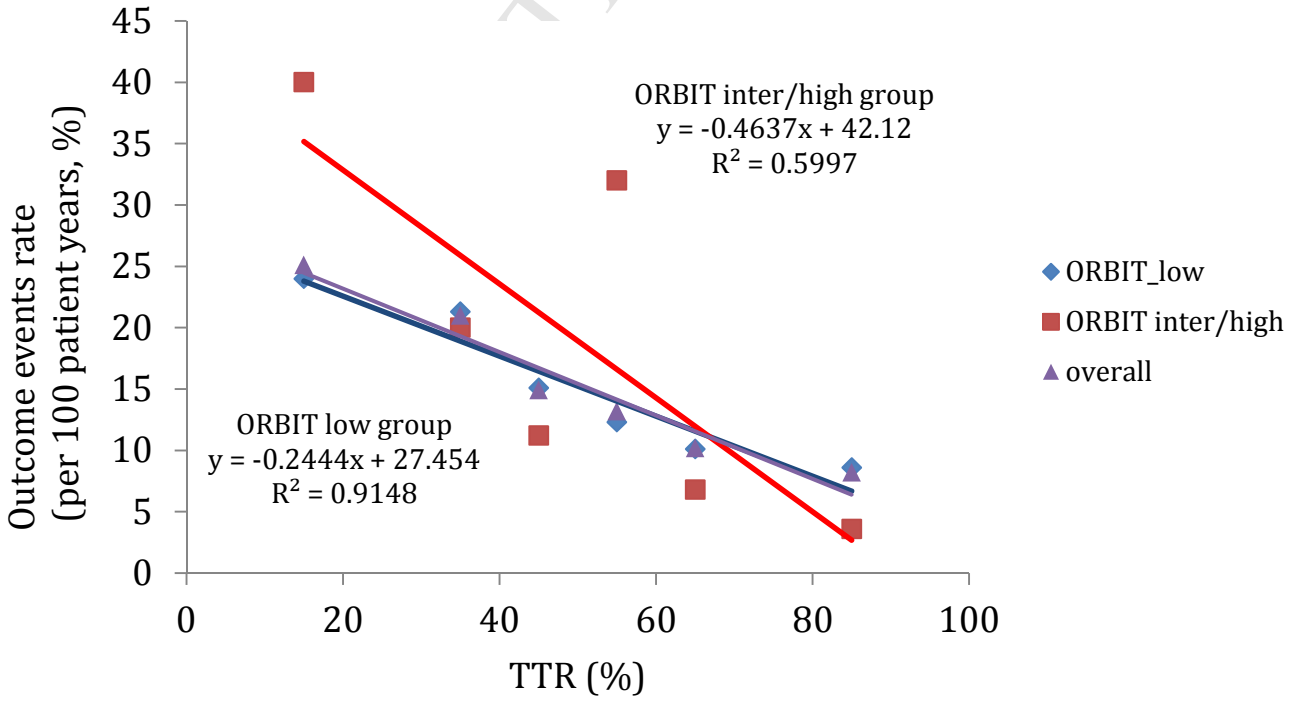
AUC; area under the curve, CI; confidence interval, SE; standard error

Figure 3 Any clinically relevant bleeding in relation to tertiles of Time to Therapeutic Range (TTR) and TTR as a continuous variable, by ORBIT and ATRIA scores

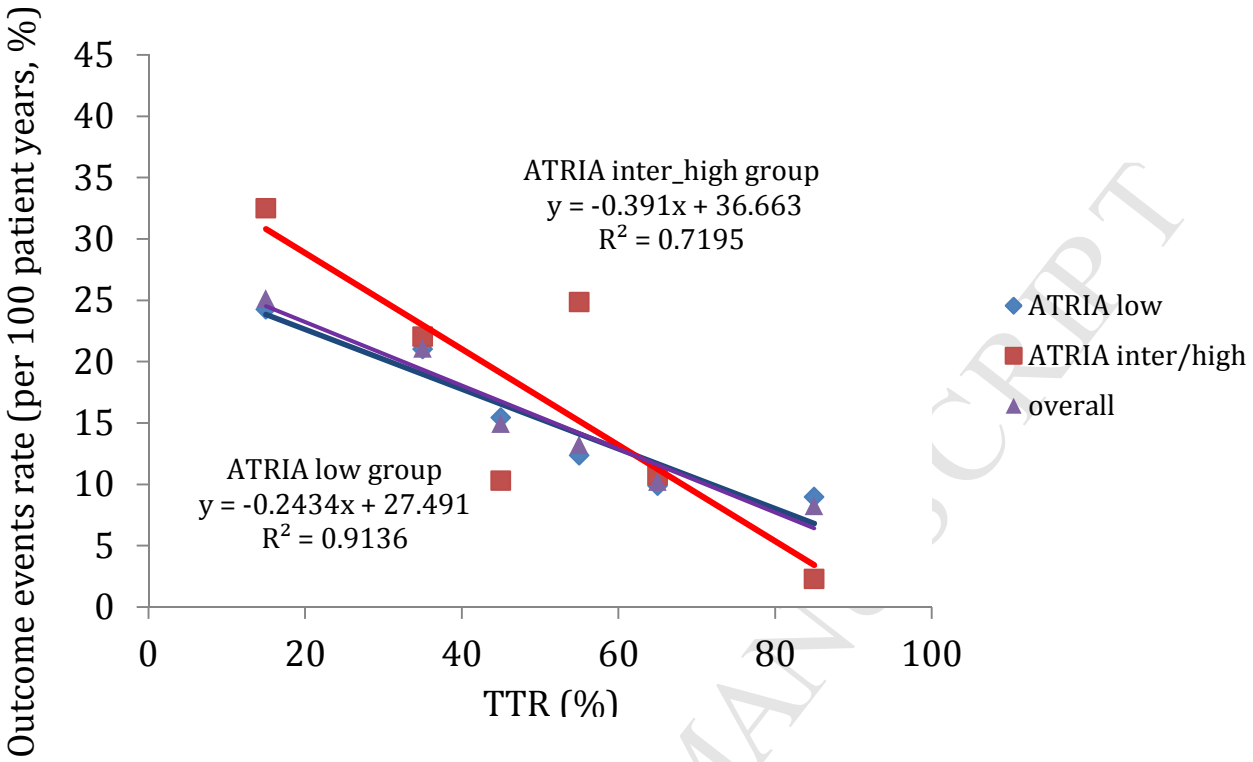
(a) TTR by tertiles of TTR



(b) TTR as a continuous variable, vs ORBIT score



(c) TTR as a continuous variable, vs ATRIA score



Clinical significance

- In this study, the HAS-BLED score performed significantly better than the ATRIA and ORBIT scores, in predicting clinically relevant bleeding.

- Quality of anticoagulation control (as reflected by time in therapeutic range,TTR) was strongly correlated with clinically relevant bleeding events in patients assessed by both ATRIA and ORBIT scores (which do not consider TTR).

- Improvements in both ATRIA and ORBIT score prediction performances were achieved by adding TTR to both scores.